REMARKS

Applicant respectfully requests reconsideration. Claims 1-5, 8-20,and 27-41 are pending for examination with claims 1 and 13 being independent claims. Claims 13-16 and 31-41 have been allowed by the Examiner. No new matter has been added.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1-5, 8-12, 17-20, 27-30 under 35 U.S.C. §103(a) as being unpatentable over Tanzi et al. (US Patent 6,365,414) in view of Selkoe et al. (Alzheimer's Disease: Insolubility of Partially Purified Helical Filaments in Sodium Dodecyl Sulfate and Urea; Science 215: 1243-1245 (1982)). Applicant respectfully traverses the rejection.

The Examiner rejected claims 1-5, 8-12, 17-20, and 27-30 based on the teaching of Tanzi et al. in view of Selkoe et al. The Examiner asserts at pages 3 and 4 of the Office Action mailed August 26, 2009 that Tanzi et al. disclose an *in vitro* system for determining formation of Aβ amyloid and that Selkoe et al. disclose subjecting samples of AD patients to urea and SDS and found that certain amyloid-like fibrils and protein aggregates (partially purified helical filaments) present in the sample are insoluble to urea and detergent.

Although Tanzi et al. describes assays of *in vitro* formation of an Aβ amyloid from Aβ peptides, and Selkoe et al. discloses that purified helical filaments (PHFs) are insoluble in detergents or urea, the combined teaching of the references fails to teach or suggest the claimed methods of contacting a sample with a detergent or urea and then using filtration to retain and detect detergent- or urea-insoluble amyloid-like fibrils or protein aggregates from a sample. One of ordinary skill in the art would have not been motivated to combine the Tanzi et al. and Selkoe et al. teaching to pre-treat samples suspected of containing amyloid-like fibrils and protein aggregates, prior to filtering, capturing and determining the presence of insoluble amyloid fibrils and protein aggregates using the method of Tanzi et al.

A *prima facie* case for obviousness must include a showing of a "teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention." [*In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)]. The Examiner does not provide teaching, suggestion or motivation to combine the references. In addition, even if

the teachings were combined, the combination fails to teach each element of the invention as claimed.

Tanzi et al. describes mixing Aβ peptides with a heavy metal such as zinc to form β amyloid. Selkoe et al. discloses that paired helical filaments (PHF) are insoluble in various detergents (SDS, urea, etc). The Examiner states at page 4 of the Office Action that it would have been obvious to combine the teaching of these references to make the claimed invention "because Tanzi specifically taught that amyloid-like fibrils are highly insoluble and Selkoe confirmed such high insolubility by treatment with urea and SDS." This is clearly not a sufficient motivation to meet the requirements of the law as expressed in KSR International Co. v. Teleflex Inc.. According to the examination guidelines issued by the USPTO:

> The Court quoting In re Kahn stated that " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " KSR International Co. v. Teleflex Inc., 550 U.S. at ___, 82 USPQ2d at 1396.
>
> "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." Id. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

The Examiner has failed to provide an "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" as is required. Id. The finding by Tanzi et al. that amyloid-like fibrils are highly insoluble and the finding by Selkoe et al. that PHFs are insoluble by treatment with urea and SDS, are not sufficient reasons to combine the cited prior art references. More specifically, the reasons proffered by the Examiner are not "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." Id. (emphasis added). The Examiner's statement that Tanzi et al. describes filtering reactions and subjecting the filtrate to tests to determine the amount of conversion of Aβ peptides to β amyloid, and that Selkoe et al. discloses

that PHF is insoluble does not articulate a reason why one of skill in the art would combine the references and is not a sufficient basis for an obviousness rejection.

Applicant additionally submits that although the Tanzi et al. and Selkoe et al. publications both reference Alzheimer's disease, the Tanzi et al. methods are drawn to Aβ peptides and Aβ amyloids, whereas the Selkoe et al. publication focused on "paired helical filaments" (PFHs). Aβ amyloids and Aβ peptides have different characteristics than tau protein and PFHs. At the time the instant invention was made, it was known in the art that paired helical filaments consist of the microtubule-associated protein tau. Applicant includes herein, a copy of a publication by Spillantini et al. *acta Neuropathol* (1996) 92:42-48, in which a clear distinction is made between β-amyloid deposits and PFHs, with the latter described in the abstract as being "made of" the hyperphosphorylated microtubule-associated protein tau. Spillantini et al. clearly distinguishes between Aβ amyloid and PFHs and additionally discloses that that β-amyloid deposits are found in an extracellular location (page 42, top of col. 1), whereas PHFs are located intracellularly (Abstract). Applicant submits that the Examiner has not set forth a motivation for one to combine a finding that PHF is insoluble in urea or SDS with the Aβ amyloid and Aβ peptide assay methods of Tanzi et al. to make the claimed invention.

The combination of the teaching of the references, as set forth by the Examiner, also fails to teach all elements of the claimed invention. In support of the obviousness rejection, the Examiner cited specific sections of the Tanzi et al. publication but Applicant submits that the cited sections do not appear to support conclusions reached by the Examiner. Tanzi et al. does not provide a clear or unambiguous disclosure of detecting whether amyloid-like fibrils or aggregates are retained on a filter as required by step (b) of the claimed invention. For Example, at page 3 of the Office Action, the Examiner cites Tanzi at col. 9, line 66 to col. 10, line 28 and lines 50-56, as teaching that "[A]myloid fibrils are retained on the filter and stained with amyloid staining dye such as Congo Red so as to be detected using electron microscopy". Applicant submits that Tanzi et al. at col. 9, line 66 to col. 10, line 28 and lines 50-56 does not describe retention of amyloid fibrils on a filter and detecting the retained amyloid, e.g. via staining of the retained amyloid with dye.

Tanzi et al. at col. 9, line 66 to col. 10, line 28 discloses that a biological sample from a subject is titrated in a serial dilution. Aβ peptide is added to the diluted samples, which are then contacted with a heavy metal cation such that Aβ peptides form Aβ amyloid. The Tanzi et al. reference then states at col. 10, lines 16-21, that: "The Aβ amyloid can then be collected by pelleting them through centrifugation. Finally, the pellets are stained using an amyloid-staining dye such as Congo Red, and the pellets are observed under microscope and quantitated (if desired) using a grid." Tanzi at col. 10, lines 50-56, mentions filtering reaction mixtures (of Aβ peptides and heavy metals) to compare amounts of peptide or amyloid, but provides no teaching or suggestion that filtration would permit detection of amyloid-like fibrils or aggregates that had been retained on the filter as require by step (b) of independent claim 1.

The Examiner also states in the Office Action that Tanzi et al., at col. 8, lines 18-33 and col. 9, lines 31-37 and 54-61, teaches "filtering a biological sample which contains Aβ amyloid fibrils on a cellulose acetate membrane or nitrocellulose filters". Applicant submits that the cited sections mention pre-filtration of $A\beta_{1-40}$ peptides that are in water using cellulose acetate, which is a step that is quite different than filtering a sample containing Aβ amyloid. Tanzi et al. mentions cellulose acetate in reference to the pre-filtering of Aβ peptides and refers to a different step of "filtering again" that follows reaction of the peptides with a heavy metal and anti-amyloidotic agent. Tanzi et al. does not disclose a type of filter for use in a "filtering again." step. Thus, in contrast to the Examiner's conclusion, Tanzi et al. do not disclose filtration of Aβ amyloid fibrils using cellulose acetate or nitrocellulose filters.

Additionally, to support the obviousness rejection, the Examiner stated at page 3 of the Office Action that "Alzheimer's disease is known to be associated with multiple polyglutamine expansions (Abstract)." Applicant respectfully submits that there is no mention of polyglutamine expansions in Tanzi et al. and that the Examiner has not provided evidence that one of skill in the art would consider Alzheimer's disease to be a polyglutamine associated disease, or that the teaching of Tanzi et al. in combination with Selkoe et al., would result in the claimed invention.

The Examiner has failed to put forth a *prima facie* case for obviousness. No motivation to combine the references has been shown. In the absence of impermissible hindsight, one

would not combine the teachings of the references to make the invention as claimed. In addition, the Examiner has not has shown that each element of the claimed invention is taught by the combination of the Tanzi et al. and Selkoe et al. references.

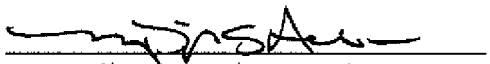
Accordingly, withdrawal of the rejection of claims 1-5, 8-12, 17-20, and 27-30 under 35 U.S.C. §103(a) as obvious is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. V0179.70001US00.

Respectfully submitted,

By: 

MaryDilys S. Anderson, Ph.D.,
Reg. No. 52,560
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: V0179.70001US00
Date: February 26, 2009

1471161